REMARKS/ARGUMENTS

Claims 28-35 and 38-40 are pending in this application.

I. Claim Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Pargraph

Claims 28-35 and 38-40 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility." (Page 2 of the instant Office Action).

Claims 28-35 and 38-40 also remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 32 of the instant Office Action).

Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the polypeptides of Claims 28-35 and 38-40 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without any further experimentation.

The gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the PRO1759 polypeptides

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the claimed PRO1759 polypeptides for the reasons previously set forth in Applicants' Responses filed on February 2, 2005, July 21, 2005 and November 30, 2005, and in the Preliminary Amendment filed August 7, 2006.

Furthermore, as first discussed in Applicants' Response of February 2, 2005, Applicants respectfully submit that Applicants rely on the gene amplification data for patentable utility of the claimed PRO1759 polypeptides, and that the gene amplification data for the gene encoding the PRO1759 polypeptide is clearly disclosed in the instant specification under Example 143. As previously discussed, ΔCt value of at least 1.0 was observed for PRO1759 in at least three of the tumors listed in Table 8. PRO1759 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$ fold amplification or 2.16 fold to 2.85-fold amplification in lung tumors

HF000842 and HF001296, and in colon tumor center HF000795. (See Table 8 of the specification).

Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO1759 polypeptide is significantly amplified in lung and colon tumors. Thus one of ordinary skill in the art would find it credible that PRO1759 has utility as a diagnostic marker of lung and colon tumors.

The Examiner has asserted that "the instant specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon)." (Page 4 of the instant Office Action).

Applicants submit that the Examiner seems to have applied a heightened utility standard in this instance, which is legally incorrect. Applicants have shown that the gene encoding PRO1759 demonstrated significant amplification, from 2.16 to 2.85 fold, in three lung and colon tumors. As explained in the Declaration of Dr. Audrey Goddard (submitted with the Response filed February 2, 2005):

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample **is significant** and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. (Emphasis added).

By referring to the 2.16-fold to 2.85-fold amplification of the PRO1759 gene in lung tumors as "very small," the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Appellants respectfully draw the Board's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state that:

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Thus, given the absence of any evidence to the contrary, Applicants maintain that the 2.16 to 2.85-fold amplification disclosed for the PRO1759 gene is significant and forms the basis for the utility claimed herein.

The Examiner further asserts that "the gene amplification data presented in the specification were problematic. The control DNA appeared to be from blood rather than from a matched tissue sample (i.e., healthy lung and colon), while the literature shows that matched tissue samples are the standard (Pennica et al.)." (Page 4 of the instant Office Action).

Applicants respectfully submit that the Examiner's statement is scientifically and factually inaccurate, because the negative control taught in the specification was known in the art at the time of filing, and accepted as a true negative control as demonstrated by use in peer reviewed publications, **including** Pennica *et al.* Pennica *et al.* explain that "[t]he relative WISP gene copy number in each colon tumor DNA was compared with **pooled normal DNA** from 10 donors by quantitative PCR" (page 14720, col. 2; emphasis added). Pennica *et al.* further explain that DNA was isolated from "the pooled blood of 10 normal human donors" (page 14718, col. 1). Thus Pennica *et al.* used the **same** control for their gene amplification experiments as that described in the instant specification.

In further examples, Pitti *et al.* (Exhibit F submitted with the Response filed February 2, 2005), used the same quantitative TaqMan PCR assay described in the specification to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. As described, Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumours, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1; emphasis added). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.* (Exhibit G submitted with the Response filed February 2, 2005), the authors used the quantitative TaqMan PCR assay to study gene amplification of *myc*, *ccnd1* and *erbB2* in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2), thus confirming the validity of the negative control. Accordingly, the art demonstrates that pooled normal blood samples are considered to be a valid negative control for gene amplification experiments of the type described in the specification.

The Examiner further asserts that "the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen). Therefore, it is not clear that the reported amplification is significant." (Page 4 of the instant Office Action). No evidence is cited in support of the assertion that aneuploid DNA is found in normal tissue. To the contrary, Sen, the only reference cited by the Examiner, teaches that aneuploidy is "a discrete chromosome mutation event that contributes to malignant transformation and progression process" (Abstract). Sen further teaches that "[i]n addition to being implicated in tumorigenesis and correlated with distinct tumor phenotypes, chromosome aneuploidy has been used as a marker of risk assessment and prognosis in several other cancers" (page 84, col. 1). Therefore, aneuploidy is a useful marker for a cancerous or pre-cancerous state. Hence, Applicants respectfully submit that whether a pre-cancerous or tumor sample were analyzed, the showing of increased PRO1759 DNA levels as a result of aneuploidy would still be significant, since it would lead to the diagnosis of either a pre-cancerous state or a cancerous state, which is the utility asserted here.

Applicants further submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed February 2, 2005),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Finally, the Examiner asserts that "[o]ne cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates." (Page 4 of the instant Office Action). Applicants note that the data in the specification relates to amplification of DNA, not mRNA, thus transcription rates would not affect this data.

A *prima facie* case of lack of utility has not been established

The Examiner asserts that "the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon)....However, there is no evidence regarding whether or not PRO1759 mRNA or polypeptide levels are also increased in these cancers. Furthermore, what is often seen is a lack of correlation between DNA amplification and increased peptide levels." (Page 6 of the instant Office Action). In support of these assertions, the Examiner refers to previously cited papers by Pennica *et al.*, Haynes *et al.*, Chen *et al.*, Hu *et al.*, Madoz-Gurpide *et al.*, Celis *et al.*, Steiner *et al.* and Feroze-Merzoug *et al.*

Applicants respectfully remind the Examiner that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter, such that the amplification of every possible gene inevitably results in protein over-expression. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

The Examiner asserts that "Pennica et al. and Sen et al. establish that gene amplification is a general feature of cancer, and that it is not predictable that the amount of amplification seen for PRO1759 is predictive of protein levels." (Page 6 of the instant Office Action). Applicants respectfully submit that, for the reasons previously set forth in Applicants' Response filed on February 2, 2005, the teachings of Pennica *et al.* are specific to *WISP* genes, and say nothing about the correlation of gene amplification and protein expression in general. Applicants further submit that Sen focuses on aneuploidy and changes in gene copy numbers in cancer, but says nothing about the correlation of gene amplification with protein expression.

The Examiner reiterates the previous discussions of Haynes *et al.*, Chen *et al.*, Hu *et al.*, Madoz-Gurpide *et al.*, Celis *et al.*, Steiner *et al.* and Feroze-Merzoug *et al.* in support of the assertion that "the state of the art is such that polypeptide levels cannot be accurately predicted

from protein levels." (Page 8 of the instant Office Action). Applicants respectfully submit that, for the reasons previously set forth in Applicants' Preliminary Amendment filed on August 7, 2006, the arguments presented by the Examiner in combination with the Haynes, Hu,Chen, Madoz-Gurpide, Steiner, Celis and Feroze-Merzoug papers, do not provide sufficient reasons to doubt the statements by Applicants that PRO1759 has utility. As previously discussed, the law does not require the existence of a "necessary" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately predicted." According to the authors themselves, the data in the above cited references confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein.

The Examiner asserts that "Haynes et al., Feroze Merzoug, and Madoz Gurpide et al. indicate that mRNA levels do not predict protein levels." (Page 10 of the instant Office Action). As previously discussed, these references may teach that protein levels cannot be "accurately predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Applicants respectfully submit that the PTO's emphasis on the need to "accurately predict" the exact "amounts" of protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predicts protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

The Examiner further asserts that "the specification of the instant application does not teach a change in DNA, mRNA or protein level of PRO1759" because "[t]here are no teachings in the specification as to the differential expression of PRO1759 DNA, mRNA, or protein in the progression of colon or lung cancers or in response to different treatments of hormones (for example)." (Page 10 of the instant Office Action). The PTO is focusing on a distinction without a difference. It is well known that cancers arise from the transformation of normal tissue cells to cancerous cells, thus the observed differences in gene copy number and gene expression between

normal and cancerous tissues are in fact the result of previously occurring changes. As discussed above, the disclosed assay is a comparative one, where what is important is that a significant difference in expression between tumor and non-tumor tissue is (or is not) observed. It is precisely this difference in DNA copy number that is demonstrated by the assay disclosed in Example 143.

The Examiner refers to the previously cited reference by Gygi *et al.*, to the effect that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data." (Page 11 of the instant Office Action). As discussed in the Preliminary Amendment filed August 7, 2006, Gygi *et al.* clearly teach that "there was a general trend of increased protein levels resulting from increased mRNA levels." (Emphasis added. See page 1726, left column, second paragraph and Figure 5). Gygi *et al.* further state that the "correlation coefficient for the whole data set (106 genes) was 0.935." While Gygi *et al.* may teach that protein levels cannot be "accurately predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels, a showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

The Examiner asserts that Futcher *et al.* "admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion." (Page 12 of the instant Office Action).

As discussed in the Preliminary Amendment filed August 7, 2006, Futcher *et al.* point out that "the different conclusions are also partly due to different methods of statistical analysis, and to real differences in data." In particular, Futcher *et al.* note that Gygi *et al.* used an inappropriate correlation coefficient in the analysis of their data. When the correct statistical methods were applied to the data of Gygi *et al.*, a good correlation was seen.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out

very small spots from the gel, and because of difficulties in background subtraction for small, weak spots.

In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo***" (page 7367, col. 2; emphasis added).

The Examiner asserts that Feroze-Merzoug *et al.* does not discuss "accurately predicting" protein expression, and that "even though Feroze-Merzoug *et al.* do not examine the expression of PRO1759 of the instant application, the teachings of Feroze-Merzoug *et al.* clearly indicate that *mRNA levels do not predict protein levels*." (Pages 12-13 of the instant Office Action; emphasis added).

Applicants respectfully submit that, as discussed in the Preliminary Amendment filed August 7, 2006, Feroze-Merzoug *et al.* looked specifically at androgen regulated genes, which are not necessarily associated with cancer. The expression of these genes clearly involves different biological process than in lung or colon tumor development. Therefore, even if the teaching of Feroze-Merzoug *et al.* accurately reflects the correlation between mRNA and protein for the particular system studied, it does not apply to the lung and colon cancer diagnostic assays of the present application. Applicants note that the emphasis on the need to be able to "predict" protein expression levels from mRNA levels is clearly expressed in the italicized quoted from the instant Office Action; as discussed above, this emphasis is inappropriate.

The Examiner asserts that Chen *et al.* clearly state that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples." (Page 13 of the instant Office Action). Applicants have already addressed this issue in the Preliminary Amendment filed August 7, 2006. Applicants repeat that a review of the correlation coefficient data presented in the Chen *et al.* paper indicates that it is more likely than not that

increased mRNA expression correlates with increased protein expression. A review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, at least 22 genes had one isoform showing a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a significant positive correlation [as determined by the authors] for at least one isoform. No genes showed a significant negative correlation. It is not surprising that not all isoforms for each gene positively correlate with mRNA expression. As the PTO may be aware, some isoforms are likely non-functional proteins. Thus, Table II further supports Applicants' assertion that it is more likely than not that protein levels correlate with mRNA expression levels.

With respect to Applicants' argument regarding Beer *et al.*, the Examiner asserts that "the specification of the instant application does not disclose any special feature, stage, or prognosis of lung tumors or colon tumors that amplify the PRO1759 gene compared to lung and colon tumors that do not amplify the PRO1759 gene." (Page 14 of the instant Office Action)

Applicants fail to see why the present specification must disclose the same amount and same type of information as in Beer *et al.* Beer *et al.* was cited to show the reliability of the microarray assay and the existence of a correlation between increased mRNA levels in tumors and increased protein levels. As Beer *et al.* has already established the existence of a general correlation between increased mRNA levels in tumors and increased protein levels, Applicants do not need to disclose the same kind or amount of data as in Beer *et al.* to further prove Beer *et al.*'s conclusion. Instead, Applicants can simply rely on the conclusion of Beer *et al.* In addition, Applicants emphasize that neither the case law nor the Utility Guidelines requires that Applicants must disclose the same amount of experimental data in a patent application for the purpose of establishing a patentable utility as in an article published in a peer-reviewed journal, where extensive experimental details are typically provided. On the contrary, as discussed in the previously filed Preliminary Amendment, the Office personnel must treat as true a statement of fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt

the credibility of such a statement. One of ordinary skill in the art would not have a legitimate basis to doubt the credibility of the results of the present microarray assay because Beer *et al.* has established the reliability of microarray data in general.

The PTO further asserts that Beer *et al.* complement their DNA microarray expression studies with northern blot hybridization and immunohistochemistry experiments for three arbitrarily selected genes with high expression, while the instant specification does not complement PRO1759 gene expression data with any other mRNA or protein studies. (Page 15 of the instant Office Action).

Applicants respectfully point out that Beer *et al.* never suggest that microarray data must be confirmed by additional mRNA or protein expression studies. Beer *et al.* simply further tested the protein or mRNA expression of the identified genes in the microarray analysis with other techniques available in the art, such as Northern blot and immunohistochemistry. It turned out that the test results obtained from these techniques were consistent with the observation in the microarray analysis, confirming that microarray analysis is a very reliable tool for studying gene expression regulation. This reliability having been confirmed by, among others, Beer *et al.*, it is not necessary for every subsequent microarray analysis to repeat the same confirmatory experiments.

The Examiner next refers to the previously cited papers by Madoz-Gurpide *et al.*, Celis *et al.* and Steiner *et al.*, again in support of the assertion that "polypeptide levels cannot be accurately predicted from mRNA levels." (Page 16 and page 17 of the instant Office Action). As discussed above, this is not the relevant issued.

The Examiner also focuses on whether "numerous alterations may occur in proteins that are not reflected in changes at the mRNA level." (Page 16 of the instant Office Action). Applicants emphasize that Applicants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. Furthermore, as discussed in Applicants' previous Responses, the cited references make clear that proteomic techniques are useful to obtain information beyond expression levels, such as the protein's activation state, posttranslational modifications, and subcellular localization. For example, Madoz-Gurpide *et al.* explain that mRNA expression alone does not provide information regarding "activation state,

post-translational modification or localization of corresponding proteins" (page 168, col. 1). Celis *et al.* note that "proteomics addresses problems that cannot be approached by DNA analysis, namely, relative abundance of the protein product, post-translational modification, subcellular localization, turnover, interaction with other proteins as well as functional aspects" (page 6, col. 2). As quoted by the Examiner, Steiner et al. state that "protein profiling of expressed genes in tissues and cells is more likely to lead to a better understanding of cellular regulation, give better insight into disease." (Pages 17-18 of the instant Office Action). While this additional information may be useful in elucidating the detailed biological function of a protein, **it is not required to establish utility of a protein as a marker for cancer**, because the claimed PRO1759 polypeptides can be used in cancer diagnosis without any knowledge regarding the function or cellular role of the polypeptides.

Applicants further submit that significant correlations between gene and protein expression are most likely to be observed for genes associated with cancer, since as Celis *et al.* note, "transformation resulted in the abnormal expression of normal genes, rather than in the expression of new ones" (page 11, col. 1). Accordingly, alterations in gene amplification or expression are more likely to be associated with altered protein expression in the case of cancer than in other cases where DNA microarrays are used (for example, the study of androgen-regulated genes described in Feroze-Merzoug *et al.*), because, as explained by Celis *et al.*, the alterations in expression levels of certain normal proteins are part of the process that leads to cancer.

The Examiner refers to the previously cited article by Hu et al. as allegedly demonstrating that because the specification "does not disclose that PRO1759 mRNA is expressed at 10-fold or higher levels compared with normal matched tissue samples ...the skilled artisan would not expect that PRO1759 protein can be used as a cancer diagnostic." (Page 19 of the instant Office Action). Applicants respectfully reiterate that Hu *et al.* did not look for a correlation between changes in mRNA and changes in protein levels, and therefore their results are not contrary to Applicants' assertion that there is a correlation between the two. Applicants are not relying on any "biological role" that the PRO1759 polypeptide has in cancer for its asserted utility. Instead, Applicants are relying on the overexpression of PRO1759 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study

means that genes with a less than five-fold change in level of expression in cancer cannot serve as a diagnostic marker of cancer.

The Examiner asserts that "Applicant is holding Hu *et al.* to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc." (Page 19 of the instant Office Action). Applicants note that they do not argue that Hu *et al.* lacks reproducibility, standard error rates, etc. for their data, given that Hu *et al.* did a literature survey and conducted no actual experiments of their own. Rather, Applicants' point is that, given the various biases in selecting the data to be considered, as acknowledged by the authors themselves, the collection of data surveyed by Hu *et al.* simply does not demonstrate the conclusion the PTO attempts to reach concerning a general lack of correlation between microarray data and biological significance. Accordingly, Applicants respectfully submit that the Examiner has not shown a lack of correlation between microarray data and the biological significance of cancer genes.

The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica, Haynes, Hu, and Chen papers, as well as the Madoz-Gurpide, Steiner, Celis and Feroze-Merzoug papers, do not provide sufficient reasons to doubt the statements by Applicants that PRO1759 has utility. As discussed above, the law does not require the existence of a "necessary" correlation between mRNA and protein levels in all situations. Nor does the law require that protein levels be "accurately predicted." According to the authors themselves, the data in the above cited references confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed February 2, 2005) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, submitted with Applicants' Response filed February 2, 2005 shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants have further submitted, with their Preliminary Amendment filed August 7, 2006, a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA."

Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*

The Examiner asserts that "Orntoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). Orntoft et al.'s findings could only be extended to other genes in such clusters. This analysis was not done for PRO1759 in the instant specification, and so it is not clear whether or not PRO1759 is in a gene cluster in a region of a chromosome that is highly amplified." (Page 21 of the instant Office Action). Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed in Applicants' previous Responses Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Applicants note that Orntoft *et al.* also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis, and that this analysis was done on a gene by gene basis,

with the authors selecting 40 well resolved abundant known proteins for which to assess the correlation between mRNA and protein levels for each gene. The authors found that "[i]n general **there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations**. Only one gene [of the 40 examined] showed disagreement between transcript alteration and protein alteration" (page 42, col. 2; emphasis added). Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

The Examiner next asserts that "Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (Page 21 of the instant Office Action; emphasis in original). The Examiner further asserts that "Applicants has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein." (Page 21 of the instant Office Action).

As discussed above, the levels of amplification for PRO1759 were **not** "low" but significant, and ranged from 2.16-fold to 2.85-fold, in three different lung and colon tumors. Applicants also respectfully point out that the Examiner appears to be confusing DNA levels with protein levels. While the proteins studied by Orntoft *et al.* were abundant, this has nothing to do with the DNA levels observed to correlate with increased gene and protein expression. As discussed above, Orntoft *et al.* found that the level of gene amplification associated with expression changes was only around two-fold, even less than the 2.16-fold to 2.85-fold amplification observed for PRO1759. Even with these relatively low levels of gene amplification, Orntoft *et al.* found that "**[i]n most cases**, chromosomal gains detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%)" (page 40, col. 2; emphasis added). The level of correlation between DNA copy number and increased mRNA levels observed by Orntoft *et al.*, from **77-80%**, clearly meets the standard of more likely than not. Orntoft *et al.* also found a "highly significant" correlation between mRNA and protein levels, with the two data sets studied having correlations of 39/40 (**98%**) and 19/26 (**73%**) (pages 42-43).

The Examiner asserts that "Orntoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison

between genes in cancerous versus non-cancerous tissues. Thus, Orntoft et al. did not find any cancer markers." (Page 21 of the instant Office Action). Applicants respectfully point out that by comparing non-invasive to invasive carcinomas, Orntoft *et al.* found markers associated with cancer malignancy.

The Examiner also appears to misunderstand the data presented by Hyman *et al.* The Examiner asserts that "of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification." The Examiner concludes that "[t]his proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1759 would be correlated with elevated levels of mRNA." (Page 22 of the instant Office Action). Applicants respectfully submit that the Examiner appears to have misinterpreted the results of Hyman *et al.* Hyman *et al.* chose to do a genome-wide analysis of a large number of genes, most of which, as shown in Figure 2, were not amplified. Accordingly, the 2% number is meaningless, as the low figure mainly results from the fact that only a small percentage of genes are amplified in the first place. The significant figure is not the percentage of genes in the genome that show amplification, but the percentage of amplified genes that demonstrate increased mRNA and protein expression.

The Examiner further asserts that the Hyman reference "found 44% (less than half) of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate." (Page 21 of the instant Office Action; emphasis in original). Applicants submit that the 10.5% figure is not relevant to the issue at hand. One of skill in the art would understand that there can be more than one cause of overexpression. The issue is not whether overexpression is always, or even typically caused by gene amplification, but rather, whether gene amplification typically leads to overexpression.

The Examiner's assertion is not consistent with the interpretation Hyman *et al.* themselves place on their data, stating that, "The results illustrate **a considerable influence of copy number on gene expression patterns**." (page 6242. col. 1; emphasis added). In the more detailed discussion of their results, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (***i.e.*, belonged to the global upper 7% of expression ratios**) compared with only 6% for genes with normal copy number." (See page

6242, col. 1; emphasis added). These details make it clear that Hyman *et al.* set a highly restrictive standard for considering a gene to be overexpressed; yet almost half of all highly amplified transcripts met even this highly restrictive standard. Therefore, the analysis performed by Hyman *et al.* clearly shows that it is "more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner asserts that Pollack *et al.* "is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification." (Page 22 of the instant Office Action). Applicants respectfully point out that Pollack *et al.* looked at gene amplification in breast tumors and breast cancer cell lines as compared to normal leukocyte DNA (page 12963, col. 2), and using different methods from those described in Orntoft *et al.* The authors still found very similar results as in Orntoft *et al.*, reporting that "on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (Abstract). Thus the art is consistent in finding that gene amplification levels of at least 2-fold, regardless of the measurement procedures, are reliably correlated with increased mRNA expression.

Finally, the Examiner asserts that Orntoft *et al.*, Hyman *et al.* and Pollack *et al.* did not study lung or colon cancer. Applicants respectfully note that only one of the references cited by the Examiner, Chen *et al.*, was related to either lung or colon cancer. As discussed above, Tables I and II of the Chen paper demonstrates that it is more likely than not that protein levels will correlate with mRNA expression levels.

The Polakis Declarations

The Examiner asserts that the second Polakis Declaration is insufficient to overcome the utility rejection because PRO1759 does not appear in the table (Exhibit B), and allegedly "it is not clear if the results presented in the table were determined by the same methodology as presented in Example 143 of the instant specification." (Page 25 of the instant Office Action).

Applicants respectfully submit that, as discussed in their previous Responses, the standard for utility is more likely than not. Dr. Polakis' Declarations provide evidence, in the form of statements by an expert in the art, that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." The PRO1759 gene was found to be amplified in lung and colon tumors. As discussed above and in Applicants' previous Responses,

one of ordinary skill in the art would therefore expect the PRO1759 mRNA to be overexpressed in the same human lung and colon tumor samples. Accordingly, one of ordinary skill in the art would understand that the PRO1759 polypeptide would be expected (more likely than not) to be overexpressed in human lung and colon tumor samples relative to their normal human tissue counterparts, as are the majority of other molecules tested.

The Examiner appears to require Applicants to provide every single experimental detail involved in the testing of the mRNA/protein correlation according to the Polakis Declaration. Such a requirement is unreasonable because neither the law nor the Utility Guidelines requires Applicants to do so.

The Examiner further notes (at page 24 of the instant Office Action) that Dr. Polakis is employed by the assignee. Applicants respectfully submit that note the sworn Declaration of Dr. Polakis is sufficient to support Applicants' position a general mRNA/protein correlation, even if Dr. Polakis is an employee of the assignee.

The Examiner also questions "why the Declaration now refers to tumor *tissue* rather than tumor *cells*, nor what the perceived significance of this change is. (Page 26 of the instant Office Action; emphasis in original). Applicants respectfully submit that the two Declarations are not inconsistent, and that there is no grounds for the PTO's requirement that the two Declarations use the exact same wording. If an mRNA/protein correlation exists in tumor cells, most likely it will exist in tumor tissues, which are comprised of cells. It is also clear from the description provided in paragraph 4 of each Polakis Declaration that both Declarations refer to the same data set, save for the fact that Polakis II provides an update to the data referred to in Polakis I, noting that by the time of Polakis II, antibodies have now been generated to 31 tumor antigen proteins expressed from differentially expressed gene transcripts instead of the "about 30" tumor antigens at the time of Polakis I.

References cited by Applicants

In response to the submitted textbook excerpts by Alberts and Lewin, the Examiner acknowledges that the teachings of Alberts and Lewin support that the initiation of transcription is the most common point for a cell to regulate gene expression. The Examiner asserts, however, that the initiation of transcription "is not the only means of regulating gene expression" according to the teaching of Alberts. (Page 26 of the instant Office Action).

Applicants respectfully submit that the utility standard is not **absolute certainty**. Rather, to overcome the presumption of truth that an assertion of utility by an applicant enjoys, the PTO must establish that it is **more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, Applicants **do not need** to establish that transcription initiation is **the only means** of regulating gene expression in order to meet the utility standard. Instead, as long as it is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change in the transcription level of a gene gives rise to a change in translation level of a gene. Applicants note that both Alberts and Lewin make clear that it is far more likely than not that protein levels for any given gene are regulated at the transcriptional level. Alberts, for example, states that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added). In a similar vein, Lewin states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Thus, the utility standard is met.

With respect to Applicants' arguments regarding Meric *et al.*, the Examiner asserts that Meric teaches that "gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." (Page 27 of the instant Office Action).

Applicants respectfully submit that Meric simply summarizes the translational regulation of cancer cells. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled to cell cycle progression and cell growth. Meric further discusses how alterations in translation control occur in cancer. For example, variant mRNA sequences can alter the translational efficiency of individual mRNA molecules. (see Abstract). Meric further teaches that the changes in translational efficiency of a mRNA transcript depend on the mutation of a specific mRNA sequence. (Page 973, column 2 to page 974, column 1). Meric never suggests that the translation of a cancer gene is suppressed in cancer in general, and that therefore, increased mRNA levels will not, in general, yield increased protein levels. To the contrary, Meric teaches that the translation efficiency of a number of

cancer genes is enhanced in cancer cells compared to their normal counterparts. For instance, in patients with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation (page 974, column 1). Therefore the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the corresponding mRNA level. Thus Meric clearly supports Applicants' assertions that it is more likely than not that, in general, changes in mRNA levels are correlated with changes in protein levels.

With respect to the over one hundred additional references cited in Applicants' Preliminary Amendment filed August 7, 2006, the Examiner asserts that "[w]ith the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general." (Pages 27-28 of the instant Office Action).

Applicants note that the submitted references, which represent experiments conducted by a large number of different research groups, demonstrate a trend of correlation found across proteins in general, and that this trend is confirmed by an overwhelming number of experiments by different researchers, using diverse experimental designs, testing various types of tissues, under numerous biological conditions. Although only a single gene or a small group of genes was tested by each individual study group, the cumulative evidence generated by over one hundred study groups certainly establishes that it is well-accepted in the art that a general mRNA/protein correlation exists.

The Examiner further asserts that the newly cited references, with the exception of Bea *et al.* and Godbout *et al.*, do not measure gene amplification. (Page 27 of the instant Office Action). Applicants have acknowledged that the new references submitted in the Information Disclosure Statement filed August 7, 2006, focus on the correlation between mRNA expression and protein expression levels, and for the most part do not examine gene amplification. However, those few references that actually looked at gene amplification **did** find a correlation between gene amplification and increased mRNA and protein expression levels.

The Examiner asserts that "Bea et al. identified *BMI-1* gene amplification, increased mRNA, and increased protein levels in only four mantle cell lymphoma tumors." (Page 28 of the instant Office Action; emphasis in original). The Examiner further asserts that "*BMI-1* gene

alterations in human neoplasms are an uncommon phenomenon." (Page 28 of the instant Office Action).

Applicants respectfully submit that the reason "only four" mantle cell lymphomas showed a combination of increased gene expression, increased mRNA, and increased protein levels is not because most samples failed to show a correlation, but because there were only four samples showing gene amplification to start with. Of these four samples with amplification of the BMI-1 gene, all showed correlating increased mRNA and protein expression. The issue is not how common gene amplification is, nor whether mRNA and protein overexpression is always, or even typically caused by gene amplification, but rather, whether gene amplification, when it is present (as it indisputably is for PRO1759 in human lung and colon tumors) typically leads to mRNA and protein overexpression. Bea *et al.* clearly supports Applicants' assertion that gene amplification is correlated with both increased mRNA and protein expression.

The Examiner further asserts that Godbout *et al.* teaches that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." (Page 29 of the instant Office Action). Applicants respectfully submit that the passage cited by the Examiner is based upon two references from 1987 and 1992. In contrast, Applicants have made of record three more recent references, published in 2002, by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Applicants' Response filed February 2, 2005), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.*

The Examiner also cites an additional paper by Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 30 of the instant Office Action). Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article

(attached as Exhibit A), genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above the PRO1759 gene showed 2.16 fold to 2.85-fold amplification in three different lung and colon tumors, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO1759, would be expected to show a corresponding increase in transcript expression.

Based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the claimed PRO1759 polypeptides, for example, as diagnostic markers for lung and colon tumors. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

In view of the above, Applicants respectfully request withdrawal of the rejections of Claims 28-35 and 38-40 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Scope of Enablement)

Claims 28-32 and 39-40 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for the claimed variant polypeptides.

Applicants respectfully maintain the position that that Claims 28-32 and 39-40 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' Responses filed on February 2, 2005, July 21, 2005 and November 30, 2005, and in the Preliminary Amendment filed August 7, 2006.

III. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-32 and 39-40 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description for the claimed variant polypeptides.

Applicants respectfully maintain the position that that Claims 58-62 and 69-70 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously

set forth in Applicants' Responses filed on February 2, 2005, July 21, 2005 and November 30, 2005, and in the Preliminary Amendment filed August 7, 2006.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned agent at the telephone number shown below.

Although no fees are due, the Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C38**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 25, 2007

By: _____
Barrie D. Greene (Reg. No. 46,740)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2256641 v1

EXHIBIT A

Supplemental Information

Criteria for defining genomic overrepresentation and amplicons. Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 and no less than one probe with a ratio > 2.0, were considered to be amplicons. When indicated, the amplicon start and end positions were extended to symmetrically include 6 neighboring non-overrepresented probes (ratio < 1.40).

Relationship between genomic copy number and gene transcript level. The relationship between the levels of copy number and transcript changes was examined as described by Hyman et al (5). Briefly, within-slide normalized genome and transcript ratios in each cell line were log-transformed and median-centered; transcript data were also median-centered using values across 6 cell lines. For each gene, the CGH data were represented by a vector that was labeled "1" for genomic overrepresentation (including amplification) ratio greater than 1.40 and "0" for no genomic overrepresentation. Genomic copy number (including amplification) was correlated with transcript expression by using signal-to-noise statistics. A weight W was calculated for each gene: $W= (mg_1 - mg_0)/(rg_1 + rg_0)$, where mg_1, rg_1 and mg_0, rg_0 denote the means and standard deviations for the mRNA levels for genomic overrepresentation and non-

overrepresentation of the cell lines, respectively. To assess the statistical significance of each weight, 10,000 random permutations of the label vector were generated. The probability that a gene had a larger or equal weight by random permutation than the original weight was denoted by α, A low α (< 0.05) indicates a strong association between genomic overrepresentation and transcription.

Fig. 1S. 2D gel images of normal bronchial epithelial cells and lung adenocarcinoma cells (cell line H522). The red cycles indicate the up-regulated proteins in H522 cancer cell line.

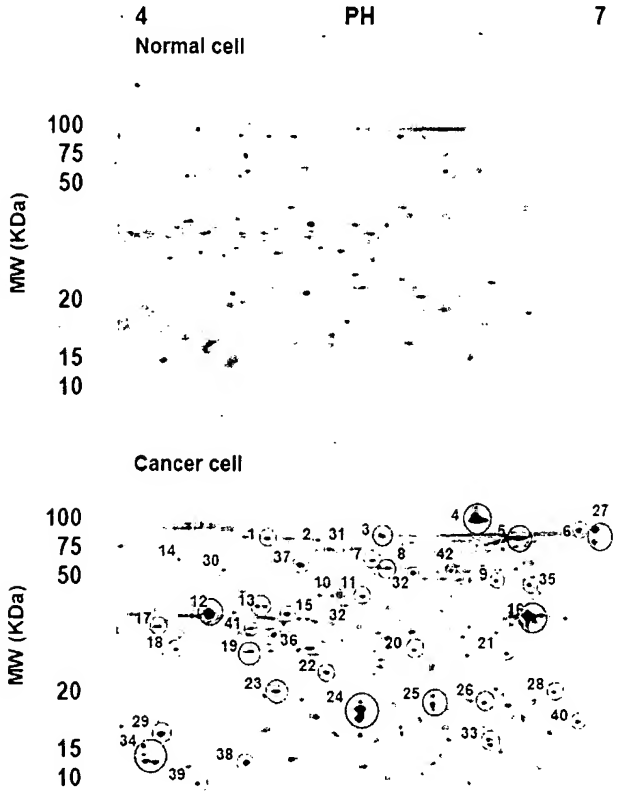

Fig. 2S. Cropped 2D gel images of selected proteins in normal bronchial epithelial cells and lung adenocarcinoma cells. Images were cropped from 2D gels of individual cell lines run between pH 4 and pH 7.

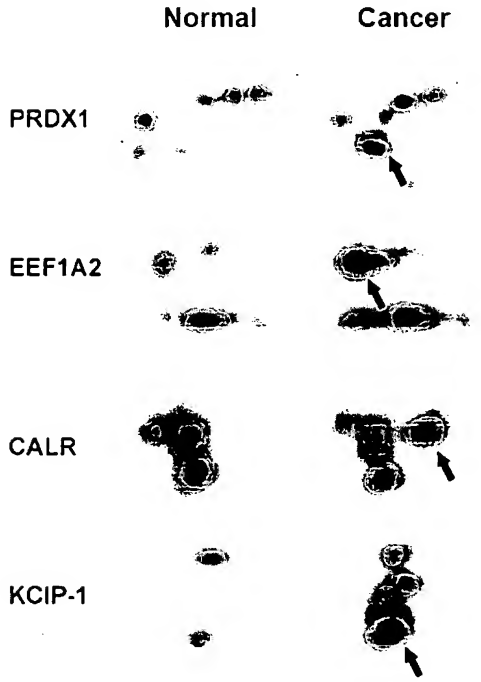

Fig. 3S. Confirmation by Southern, northern, and western blot analyses of increased DNA copies, transcript levels, and protein levels in the genes identified in high-throughput microarray and proteomic analyses revealed close correlations in the extent of changes in gene copies, transcript, and protein of each of the four genes in the cancer cell lines. Each experiment was repeated at least three times. Bars indicate SDs of the mean of three individual experiments.

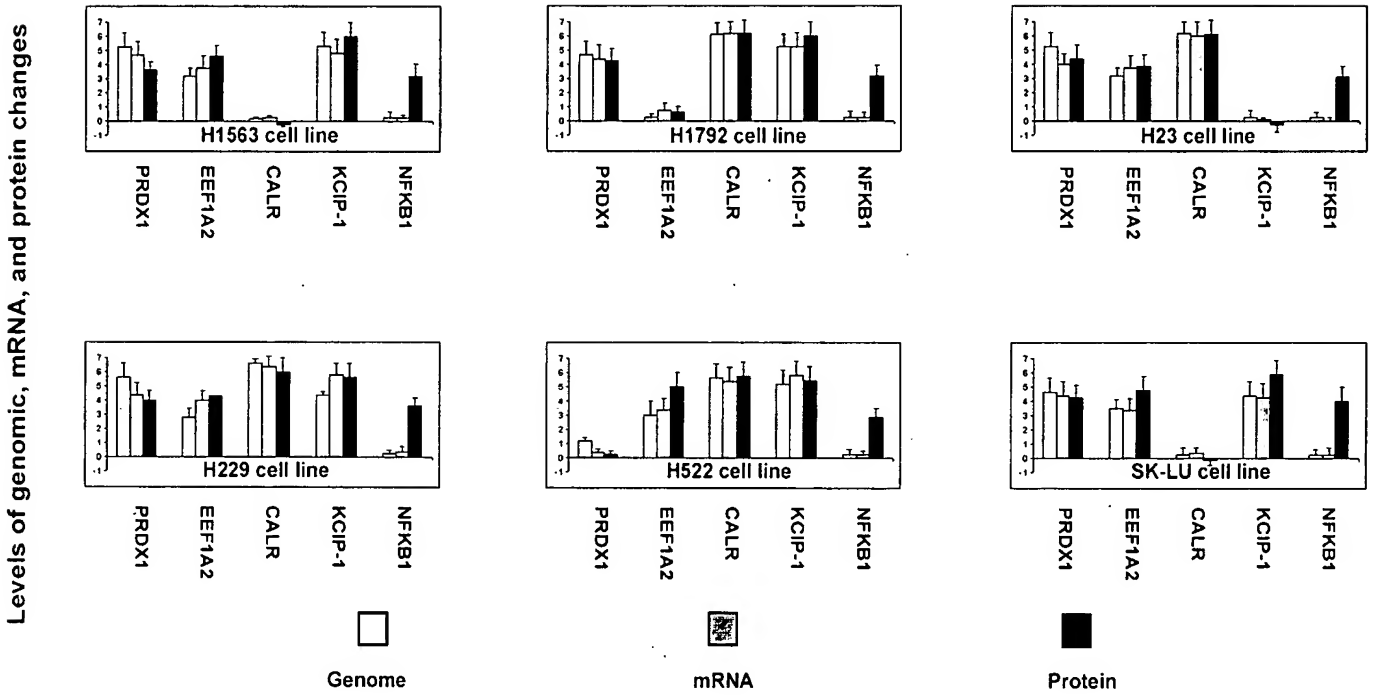

Fig. 4S. siRNAs against EEF1A2 or KCIP-1 specifically inhibit its expression, respectively. (*A*) Lung cancer cells were transfected with EEF1A2-siRNA , scrambled siRNA, or PBS. Western blot analysis of protein expression was performed 48 h after transfection. The same filter was probed with β-actin antibody to control for even loading. (*B*) Lung cancer cells were treated with KCIP-1 -siRNA , scrambled siRNA, or PBS. Western blot analysis of protein expression was performed 48 h after transfection.

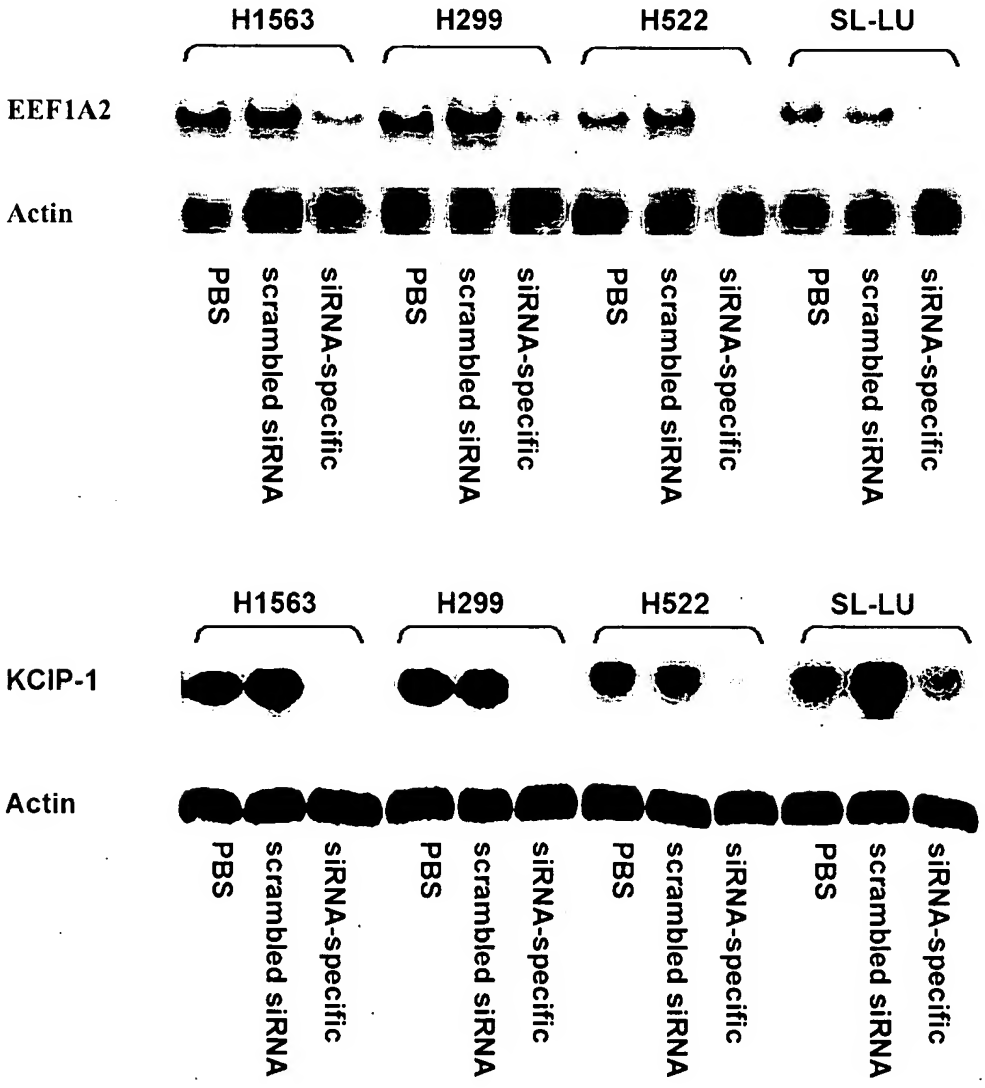

Fig. 5S. Effect of EEF1A2 or KCIP-1 depletion on cell proliferation. The viability of cells at 48 after transfection was determined by MTT staining to examine the effect of siRNA transfection on cancer cell proliferation. The growth rate was expressed as the percentage of viable EEF1A2-siRNA3-tranfected cells (A) and KCIP-1-siRNA3-tranfected cells (B) in relation to PBS-treated control cells and scrambled siRNA-treated cells. Bars indicate SDs of the mean of three individual experiments.

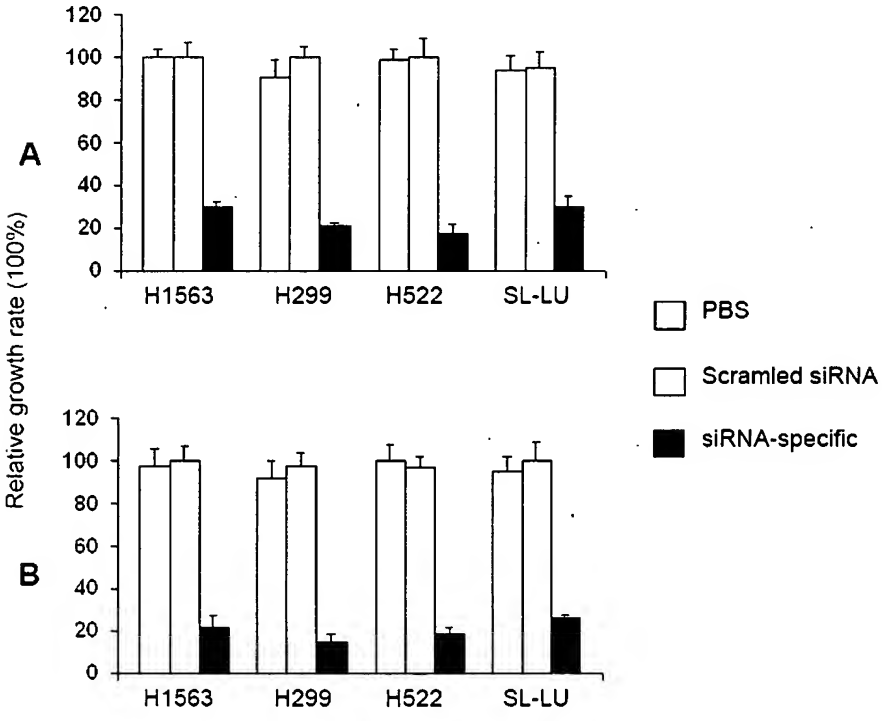

Fig. 6S. Survival analysis of 113 patients with stage 1 NSCLC based on EEF1A2 (left) and KCIP-1 (right) expression status.

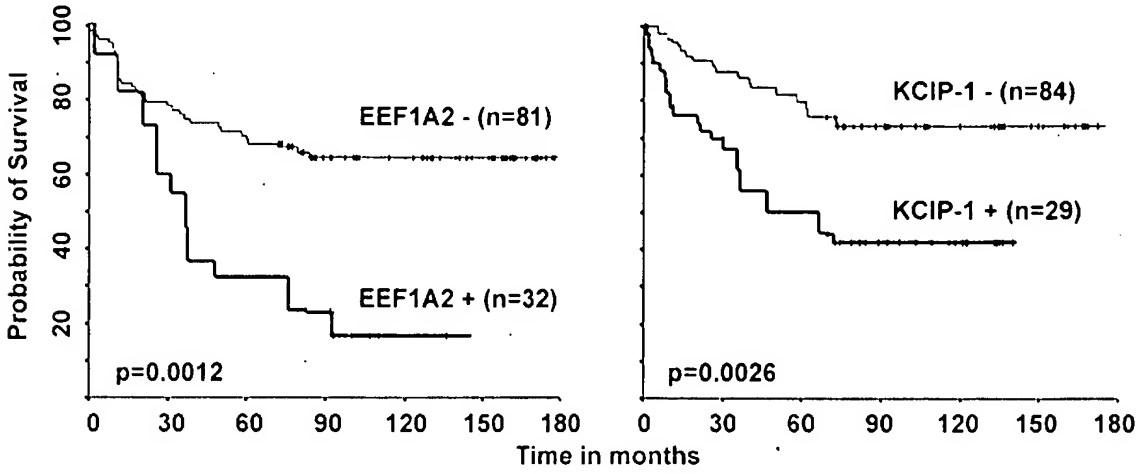

Table 1S. 587 genes with increases in DNA copy number detected by comparative genomic hybridization microarray in the lung adenocarcinoma cell lines

Genes with increased genome copy number		
Gene Symbol	Ch. loc.	Distance from p arm of chromosome (Mb)
ENO1	1	8.5
PINK1	1	20.1
DDOST	1	20.1
SMARCF1	1	26.3
SFN	1	26.4
NR0B2	1	26.5
EIF3S2	1	32.1
MLP	1	32.2
YARS	1	32.7
PDX1	1	45.4
AKR1A1	1	45.4
PRDX1	1	45.4
NASP	1	45.5
FAAH	1	46.2
UQCRH	1	46.2
RPL7	1	96.4
COL11A1	1	102.6
AMY2B	1	103.3
ECM1	1	147.3
MCL1	1	147.3
PSMB4	1	148.1
POGZ	1	148.2
S100A2	1	150.4
RAB13	1	150.7
JTB	1	150.7
RPS27	1	150.7
TPM3	1	150.9
HAX1	1	151
EFNA1	1	151.9
MUC1	1	151.9
PKLR	1	152

C1orf2	1	152
SCAMP3	1	152
PMF1	1	153
CCT3	1	153.1
MEF2D	1	153.2
CRABP2	1	153.4
PRCC	1	153.5
UAP1	1	159.2
TKT	1	159.3
ATP1B1	1	165.8
SLC19A2	1	166.1
F5	1	166.2
CHIT1	1	199.7
SNRPE	1	200.2
ACP1	2	0.255
ODC1	2	10.6 0
P5	2	10.9 0
CHST10	2	100.6 0
NPAS2	2	101.0 0
RPL31	2	101.2 0
MAP4K4	2	101.9 0
GCK	2	101.9 0
IL1R2	2	102.2 0
IL1RL2	2	102.4 0
NPHP1	2	110.4 0
BENE	2	110.4 0
BCL2L11	2	111.8 0
MERTK	2	112.6 0
RANBP2L1	2	113.0 0
SLC20A1	2	113.3 0
MGAT5	2	135.0 0
CCNT2	2	135.7 0
STAT1	2	191.8 0
STAT4	2	191.9 0
MYO1B	2	192.1 0
DNAH7	2	196.6 0
STK17B	2	197.0 0
SF3B1	2	198.2 0
PREI3	2	198.3 0

HSPE1	2	198.3 0
HSPD1	2	198.3 0
MYT1L	2	2.8 0
XRCC5	2	216.9 0
RPL37A	2	217.3 0
IGFBP5	2	217.5 0
IGFBP2	2	217.5 0
RNASEH1	2	3.2 0
RPS7	2	3.3 0
SOX11	2	5.8 0
IF	2	55.4 0
MTIF2	2	55.4 0
RPS27A	2	55.4 0
SLC1A4	2	65.2 0
RAB1A	2	65.3 0
ACTR2	2	65.4 0
RNF144	2	7.1 0
FABP1	2	88.3 0
RPIA	2	88.9 0
IGKC	2	89.0 0
ADAM17	2	9.6 0
YWHAQ	2	9.7 0
CCR2	3	46.2
LTF	3	46.3
MRAS	3	139.3
PIK3CB	3	139.7
COPB2	3	140.4
RBP1	3	140.5
RASA2	3	142.5
PFN2	3	151
SIAH2	3	151.7
H963	3	152.2
SMC4L1	3	161.4
KPNA4	3	161.5
B3GALT3	3	162.1
S100P	4	6.7
HMGE	4	7.1
ACOX3	4	8.5
CPZ	4	8.7

LIAS	4	39.3
UGDH	4	39.3
HIP2	4	39.5
FAP	4	39.8
ARHH	4	40
APBB2	4	40.7
UCHL1	4	41.1
IBSP	4	89.1
PKD2	4	89.3
SPP1	4	89.3
PET112L	4	153.1
TRIM2	4	154.7
PLRG1	4	155.9
FGG	4	156
FGB	4	156
SDHA	5	0.251
PDCD6	5	0.305
SEC6	5	0.479
SLC9A3	5	0.506
TRIP	5	0.926
TRIP13	5	0.926
CCT5	5	10.3
CTNND2	5	11
PTPRF	5	14.2
OSMR	5	38.9
FYB	5	39.1
C9	5	39.3
PTGER4	5	40.7
AAK1	5	40.8
RPL37	5	40.8
FOXD1	5	72.8
FOXD2	5	72.8
ENC1	5	74
HMGCR	5	74.7
KIF3A	5	132.1
QP-C	5	132.2
HSPA4	5	132.4
SPINK1	5	147.2
SPINK5	5	147.4

HTR4	5	147.8
MAML1	5	179.2
CANX	5	179.2
NQO2	6	3
E2F3	6	20.5
SOX4	6	21.7
HDGF	6	22.6
ITPR3	6	33.6
RPS10	6	34.6
TEF	6	35.4
RPL10A	6	35.4
RPA40	6	43.5
VEGF	6	43.7
CDC5L	6	44.4
SUPT3H	6	44.9
OSF-2	6	45.4
FSCN1	7	5.3
TRIAD3	7	5.4
MPP6	7	24.4
DFNA5	7	24.4
OSBPL3	7	24.5
CYCS	7	24.9
NFE2L3	7	25.9
HNRPA2B1	7	25.9
CBX3	7	25.9
ADCY1	7	45.3
IGFBP1	7	45.6
IGFBP3	7	45.7
HUS1	7	47.7
ZPBP	7	49.7
ZNFN1A1	7	50.1
DDC	7	50.2
WBSCR22	7	72.5
CLDN3	7	72.6
CLDN4	7	72.7
MDH2	7	75.3
HSPB1	7	75.5
DTX2	7	75.7
POMZP3	7	75.8

CALCR	7	92.7
CALR	7	92.7
GNGT1	7	93.1
TFPI2	7	93.1
BET1	7	93.2
COL1A2	7	93.6
ZFP95	7	98.7
ATP5J2	7	98.7
CYP3A5	7	98.8
CYP3A7	7	98.9
SI	7	133.6
AKR1B10	7	133.6
BPGM	7	133.7
RPS20	8	56.7
PENK	8	57.1
MET	8	57.1
LY96	8	74.6
TCEB1	8	74.6
PI15	8	75.5
LAPTM4B	8	98.5
MATN2	8	98.6
RPL30	8	98.7
POP1	8	98.8
UK114	8	98.8
STK3	8	99.1
COX6C	8	100.6
SPAG1	8	100.8
POLR2K	8	100.8
KCIP-1	8	101.6
PABPC1	8	101.78
CPN2	8	143.8
LY6H	8	144
EEF1D	8	144.4
TSTA3	8	144.5
VPS28	8	145.3
ZNF7	8	145.6
RPL8	8	145.6
PSMD5	9	117
TRAF1	9	117.1

TNF	9	117.1
TRA1	9	117.1
C5	9	117.2
CEP1	9	117.3
GOLGA1	9	121.1
RPL35	9	121.1
PPP6C	9	121.4
HSPA5	9	121.5
CIZ1	9	124.4
LCN2	9	124.4
GOLGA2	9	124.5
FUT7	9	133.4
ENTPD2	9	133.4
DPP7	9	133.4
PFKP	10	3.2
PITRM1	10	3.3
AKR1C4	10	5.1
AKR1C3	10	5.1
AKR1C1	10	5.1
CALML3	10	5.7
GDI2	10	6
CAMK2G	10	75.5
PLAU	10	75.6
ADK	10	75.8
DSP	10	76.7
VDAC2	10	76.9
TALDO1	11	0.434
DEAF1	11	0.503
KCNQ1	11	2.4
SLC22A1LS	11	2.9
SLC22A1L	11	2.9
TSSC3	11	2.9
TUB	11	8
EIF3S5	11	8
LMO1	11	8.2
RPL27A	11	8.7
ST5	11	8.8
SAA4	11	18.3
GTF2H1	11	18.4

LDHC	11	18.5
LDHA	11	18.5
CSRP3	11	19.2
HTATIP2	11	20.4
MAPK8IP1	11	45.9
HDAC2	11	46
OASIS	11	46.3
MDK	11	46.4
ARHGAP1	11	46.7
ROM1	11	62.6
B3GAT3	11	62.6
G2AN	11	62.6
EEF1G	11	62.6
BSCL2	11	62.7
STX5A	11	62.8
TAF6	11	62.8
POLR2G	11	62.8
AIP	11	67.5
DOC-1R	11	67.5
NDUFV1	11	67.6
GSTP1	11	67.6
ALDH3B2	11	67.7
MMP20	11	102.5
MMP8	11	102.6
MMP3	11	102.7
MMP10	11	102.7
MMP1	11	102.7
MMP13	11	102.8
MMP12	11	102.8
UPK2	11	118.9
G6PT1	11	118.9
HYOU1	11	118.9
SCNN1A	12	6.3
TNFRSF7	12	6.4
LTBR	12	6.4
NOL1	12	6.5
VAMP1	12	6.5
GAPD	12	6.5
GYS2	12	21.6

LDHB	12	21.7
KRT7	12	52.3
KRTHB3	12	52.4
KRTHB6	12	52.4
KRTHB1	12	52.4
KRTHB5	12	52.5
KRT5	12	52.6
KRT6E	12	52.6
IRS4	12	52.7
KRT2A	12	52.8
SOAT2	12	53.2
RAB5B	12	56.1
PA2G4	12	56.2
ERBB3	12	56.2
ATP5B	12	56.7
TEBP	12	56.8
NACA	12	56.8
PTPRR	12	70.7
TM4SF3	12	71.2
GPR49	12	71.6
CART	12	85.6
NTS	12	86.2
KITLG	12	88.8
KIT	12	88.8
ASCL1	12	103.3
TDG	12	104.3
NFYB	12	104.4
TXNRD1	12	104.6
CKAP4	12	106.6
MSI1	12	120.6
HSPC132	12	120.7
15E1.2	12	120.7
COX6A1	12	120.7
BGN	12	122.5
KNTC1	12	122.8
CD36	12	125
SCARB1	12	125
RAN	12	129.88
FZD9	12	130.4

RPL36A	14	48.1
SON	14	48.6
ATP5S	14	48.8
PGD	14	50.7
C14orf32	14	53.5
THBS2	15	37.5
SRP14	15	37.9
BUB1	15	38
BUB1B	15	38
IVD	15	38.3
TRAF4	15	38.3
C18B11	15	38.4
GCHFR	15	38.6
RAD51	15	38.6
SPINT1	15	38.7
CIB1	15	40.2
RPL17	15	45.26
SLC12A1	15	46.1
NR2E3	15	69.7
PKM2	15	70.1
AP3S2	15	88
IDH2	15	88.2
MRPL28	16	0.357
RPL23A	16	0.377
SOLH	16	0.518
PIGQ	16	0.56
RAB40C	16	0.58
MSLN	16	0.753
BAIAP3	16	1.3
UBE2I	16	1.3
CLCN7	16	1.4
MAPK8IP3	16	1.7
IGFALS	16	1.8
HAGH	16	1.8
RPL3L	16	1.9
RPS2	16	1.95
SYNGR3	16	2
MMPL1	16	3.1
CLDN9	16	3.1

PM5	16	16.3
RPS15A	16	18.7
ARL6IP	16	18.7
COQ7	16	19
GTF3C1	16	27.4
EIF3S8	16	28.3
ATP2A1	16	28.9
CD19	16	28.9
TUFM	16	28.9
TBX6	16	30.1
ALDOA	16	30.1
NME4	16	53.6
CCL17	16	57.2
GPR56	16	57.4
KIFC3	16	57.5
CDH1	16	68.5
SNTB2	16	69
NQO1	16	69.5
AARS	16	70
DDX19	16	70.1
SLC7A5	16	87.6
CA5A	16	87.7
MVD	16	88.4
CYBA	16	88.4
CBFA2T3	16	88.6
APRT	16	88.6
GALNS	16	88.6
CDH15	16	88.9
RPL13	16	89.3
MCP	17	32.4
AATF	17	35
ERBB2	17	35.11
TOP2A	17	38.5
CCR7	17	38.6
KRT12	17	38.8
KRT10	17	38.8
KRT20	17	38.9
KRTHA3A	17	39.4
KRTHA4	17	39.4

KRTHA3B	17	39.4
KRTHA5	17	39.5
KRTHA7	17	39.5
KRTHA1	17	39.5
KRTHA2	17	39.5
KRT16	17	39.5
KRT14	17	39.5
KRT17	17	39.5
KRT9	17	39.6
KRT13	17	39.6
KRT15	17	39.6
KRT19	17	39.6
HAP1	17	39.8
JUP	17	39.8
ACLY	17	39.9
CRF	17	40.39
PSME3	17	40.9
BECN1	17	40.9
G6PC	17	41
ARHN	17	41.1
RPL27	17	41.1
NME1	17	46.59
SCAP1	17	46.6
HOXB1	17	46.9
HOXB5	17	47
HOXB7	17	47
HOXB3	17	47
HOXB2	17	47
HOXB13	17	47.1
ATP5G1	17	47.3
PHB	17	47.8
ITGA3	17	48.5
SGCA	17	48.6
COL1A1	17	48.6
CHAD	17	48.9
CAV3	17	49
CACNA1G	17	49
ABCC3	17	49.1
TOB1	17	49.3

NME2	17	49.6
TOM1	17	53.3
TOM1L1	17	53.3
COX11	17	53.4
RPL38	17	72.7
SLC9A3R1	17	73.2
FDXR	17	73.3
ATP5H	17	73.5
SMT3H2	17	73.6
MSF	17	75.7
EVER1	17	76.6
TK1	17	76.6
SYNGR2	17	76.6
BIRC5	17	76.7
LGALS3BP	17	77.4
CBX4	17	78.4
MRPL12	17	80.2
PDE6G	17	80.2
P4HB	17	80.3
PCYT2	17	80.4
TGIF	18	3.4
NAPG	18	10.5
IMPA2	18	12
AFG3L2	18	12.3
PTPN2	18	12.8
CDH2	18	25.4
DSC3	18	28.5
DSG1	18	28.8
DSG3	18	28.9
DSG2	18	29
B4GALT6	18	29.1
TTR	18	29.1
MEP1B	18	29.7
PPAP2C	19	0.221
PEPD	19	38.6
GPI	19	39.55
ZNF135	19	39.8
ZNF140	19	39.8
SCN1B	19	40.2

HPN	19	40.2
ZNF146	19	41.4
ZNF345	19	42
DPF1	19	43.4
SPINT2	19	43.4
PSMD8	19	43.5
YIF1P	19	43.5
RYR1	19	43.6
SUPT5H	19	44.6
RPS16	19	44.6
BCKDHA	19	46.6
CEACAM4	19	46.8
CEACAM5	19	46.9
CEACAM6	19	46.9
CEACAM3	19	47
ATP1A3	19	47.1
RABAC1	19	47.1
GPR4	19	50.8
EML2	19	50.8
GPR19	19	50.8
GIP	19	50.8
GIPR	19	50.8
SNRPD2	19	50.9
PSCD2	19	53.6
GRIN2D	19	53.6
KDELR1	19	53.6
TNNI3	19	60.3
TNNT1	19	60.3
PTPRH	19	60.4
SYT5	19	60.4
IL11	19	60.6
RPL28	19	60.6
PEG3	19	61.9
STK13	19	62.4
ZNF272	19	62.5
SEDLP	19	62.6
ZNF211	19	62.8
ZNF134	19	62.8
ZNF154	19	62.9

ZNF274	19	63.4
ZNF8	19	63.5
ZNF132	19	63.6
RPS5	19	63.6
UBE2M	19	63.7
TRIM28	19	63.7
SRC	20	35.4
DAP	20	35.6
TGIF2	20	35.8
KIAA1219	20	37.8
TOP1	20	40.3
UBE2C	20	45.1
PRKCBP1	20	46.5
SS18L1	20	61.4
CDK3	20	61.6
RPS21	20	61.6
EEF1A2	20	62.8
URKL1	20	63.3
C20orf14	20	63.3
MYT1	20	63.5
TFF3	21	42.6
TFF2	21	42.7
TFF1	21	42.7
PDXK	21	44
CSTB	21	44.1
MIF	22	22.6
CHEK2	22	27.4
CDS1	22	27.4
XBP1	22	27.5
LGALS1	22	36.4
PRDX4	X	22.9
PFC	X	46.3
SYN1	X	46.3
TIMP1	X	46.3
PIM2	X	47.6
JM4	X	47.7
JM5	X	47.7
T54	X	47.8
LMO6	X	47.8

PLP2	X	47.8
AKAP4	X	48.7
MAGED1	X	50.3
PHKA1	X	70
RPS4X	X	71
COX7B	X	75.2
ATP7A	X	75.3
PGK1	X	75.4
GPR23	X	76.1
SSR4	X	152.6

Table 2S. Summary of amplicons in 6 lung adenocarcinoma cell lines by CGH microarray

Location	Start from p arm of each chromsome (Mb)	End from p arm of each chromsome (Mb)	Size of the Amplicon (bp)
1p36.23	7,935,153	8,990,392	1,055,239
1p36.11	26,706,664	26,924,602	217,938
1p34.1	45,645,801	45,753,660	107,859
1q21.33	150,346,660	153,583,682	3,237,022
1q24.2	165,807,605	166287379	479,774
2p25.1	3,116,230	5,792,115	2,675,885
2p25.1	9,580,011	10,903,558	1,323,547
2p11.2	88,261,772	89,459,144	1,197,372
2q11.2	100,895,131	102,103,403	1,208,272
2q32.3-33.1	191,800,000	198,190,504	6,390,504
2q35	216,797,696	217,354,662	556,966
3q22.3	139,549,237	140,591,166	1,041,929
3q25.1	151,165,392	152,403,677	1,238,285
3q25.33	161,600,132	162,305,862	705,730
4p16.1	6,812,868	8,739,550	1,926,682
4q22.2	89,077,881	89,253,981	176,100
5p15.33	271,401	971,160	699,759
5p15.2	10,303,371	17,329,943	7,026,572
5p13.1	38,881,893	40,871,072	1,989,179
5q32	147,184,339	148,013,909	829,570
5q35.3	180,348,507	180,603,502	254,995
6p22.3	20,510,377	22,679,871	2,169,494
6p21.33	2,945,207	3,102,759	157,552

7p22.1	5,405,698	6,296,940	891,242
7p15.3	24,386,241	26,026,216	1,639,975
7p13	45,701,327	47,792,486	2,091,159
7q11.23	72,542,549	75,901,214	3,358,665
7q21.3	93,159,360	93,705,195	545,835
8q22.3	98,856,461	101,804,115	2,947,654
8q24.3.	145,619,808	146,043,698	423,890
9p22.1	19,366,254	21,132,144	1,765,890
9p13.3	33,230,196	33,392,517	162,321
9q33.2	120,657,888	121,019,442	361,554
9q33.3	124,720,183	125,083,163	362,980
9q34.11	127,991,272	128,117,822	126,550
10p15.2	3,099,712	3,205,003	105,291
10p15.1	5228798	5,895,379	666,581
11p15.5	2,422,797	2,907,226	484,429
11p15.4	8,016,756	8,889,074	872,318
11p-15.1	18,209,479	20,361,904	2,152,425
11p11.2	45,863,778	46,678,696	814,918
11q12.3	62,139,345	62,356,136	216,791
11q13.2	67,030,545	67,198,753	168,208
11q21	93,866,801	93,872,392	5,591
12p13.31	6,326,276	6,547,680	221,404
12q13.13	51,148,575	54,782,854	3,634,279
12q23.2	101,853,931	105,144,375	3,290,444
12q24.31	123,787,056	123,873,214	86,158
14q21.3	49,155,159	49,872,026	716,867
15q14	37,660,567	38,937,145	1,276,578
15q23	69,889,948	70,310,738	420,790

15q23	45,268,852	45,272,849	3,997
15q26.1	88,177,793	88,446,712	268,919
16p13.3	357,397	1,984,277	1,626,880
16p13.3	3,002,207	3,004,507	2,300
16q13.2	9,762,923	10,184,112	421,189
16p12.3	18,418,684	18,998,855	580,171
16p11.2	29,989,236	30,004,583	15,347
16p21.31	34,493,211	35,546,536	1,053,325
16q22.2	68,300,807	68,890,598	589,791
16q24.2-24.3	86,421,130	88,158,450	1,737,320
17q21.2	35,798,321	37,328,798	1,530,477
17q21.31	38,215,678	41,268,973	3,053,295
17q21.33	44,836,419	46,604,103	1,767,684
17q21.33-q22	50333203	50,401,053	67,850
17q25.1	69,711,412	70,380,692	669,280
17q25.2	72,789,117	73,732,372	943,255
17q25.3	74,478,932	75,427,826	948,894
17q25.3	77,227,655	77,462,586	234,931
18p11.21	10,516,031	12,874,334	2,358,303
18q12.1	23,784,934	28,054,365	4,269,431
18q12.1	45,268,852	45,272,849	3,997
19q13.13	12,910,423	12916303	5,880
19q13.1	38,569,699	40,249,315	1,679,616
19q13.12-13.2	41,411,488	43,770,012	2,358,524
19q13.2	44,618,478	44,628,052	9,574
19q13.2	46,595,544	47,155,320	559,776
19q13.32	50,863,342	50,887,282	23,940

19q13.32	53,589,944	53,674,457	84,513
19q13.42-13.43	60,354,950	63,753,894	3,398,944
20q13.12	43,874,662	45,418,974	1,544,312
20q13.33	60,152,217	62,377,837	2,225,620
21q22.3	42,605,233	44,020,687	1,415,454
22q12.1	22,561,118	27,521,114	4,959,996
Xp22.11	21,810,216	23,464,172	1,653,956
XP11.23	47,187,558	48,787,809	1,600,251
xP11.22	49,658,442	51,478,486	1,820,044
Xq13.1	71,280,162	71,583,499	303,337
Xq21.1	71,280,162	77,818,738	6,538,576
Xq28	152,579,818	152,584,801	4,983

Table 3S. 587 genes with increased mRNA levels detected by transcript microarray in the lung adenocarcinoma cell lines

Gene Symbol	Chro.	Distance from p arm of chromosome (Mb)
ENO1	1	8.5
DDOST	1	20.1
SFN	1	26.4
MLP	1	32.2
AKR1A1	1	45.4
PRDX1	1	45.4
UQCRH	1	46.2
PABPN1	1	57.1
RPL7	1	96.4
COL11A1	1	102.6
TRIM29	1	113.1
KLF6	1	114.7
MCL1	1	147.3
PCSK2	1	147.8
PSMB4	1	148.1
S100A2	1	150.4
CALD1	1	150.5
JTB	1	150.7
RPS27	1	150.7
HAX1	1	151
MUC1	1	151.9
NQO3A2	1	152.5
CCT3	1	153.1
CRABP2	1	153.4
TKT	1	159.3
ATP1B1	1	165.8
CHIT1	1	199.7
SNRPE	1	200.2
IRS2	1	203.9
FBLN1	1	204.3
MGC9850	1	214.9
YWHAQ	2	9.6
TNNI2	2	26.3

USP9Y	2	26.9
TGFBR1	2	38.7
WNT6	2	74
GLRX	2	177.9
FAS	2	191.7
ODC1	2	10.6 0
RPL31	2	101.2 0
BENE	2	110.4 0
CCT2	2	135.7 0
STAT1	2	191.8 0
HSPD1	2	198.3 0
HSPE1	2	198.3 0
RPL37A	2	217.3 0
IGFBP2	2	217.5 0
RPS7	2	3.3 0
RAB1A	2	65.3 0
IGKC	2	89.0 0
LTF	3	46.3
PSMF1	3	52.7
HOXD9	3	101.9
UMPS	3	150.6
PFN2	3	151
KPNA4	3	161.5
S100P	4	6.7
UGDH	4	39.3
UCHL1	4	41.1
SPP1	4	89.3
EML1	4	104.1
PLAT	4	143.3
TRIM2	4	154.7
FGB	4	156
FGG	4	156
MFGE8	4	186.7
SDHA	5	0.251
PDCD6	5	0.305
CCT5	5	10.3
PTPRF	5	14.2
RPL37	5	40.8

SIAT4C	5	64.1
ENC1	5	74
QP-C	5	132.2
GTF2E1	5	132.4
BLZF1	5	133.3
RABGGTB	5	133.7
SPINK1	5	147.2
XRCC3	5	178.1
CRSP9	5	179.1
CANX	5	179.2
PMS2L1	5	198.2
SOX4	6	21.7
EFNB2	6	21.7
HDGF	6	22.6
RPS10	6	34.6
RPL10A	6	35.4
RAD23A	6	38.8
VEGF	6	43.7
OSF-2	6	45.4
DRCTNNB1A	6	64.3
ABCF1	6	159.2
FSCN1	7	5.3
FBXO11	7	5.3
CYCS	7	24.9
CG018	7	24.9
METAP2	7	24.9
CBX3	7	25.9
CRYBA1	7	26
TFCP2	7	43.9
IGFBP3	7	45.7
PLK3	7	72.7
CLDN4	7	72.7
HSPB1	7	75.5
CALR	7	92.7
PDAP1	7	93.1
COL1A2	7	93.6
ATP5J2	7	98.7
AKR1B10	7	133.6

SIAT7B	7	140.9
RPS20	8	56.7
ZW10	8	61.6
TCEB1	8	74.6
LAPTM4B	8	98.5
RPL30	8	98.7
GGTL4	8	100.9
PARD6A	8	101.2
KCIP-1	8	101.6
PABPC1	8	101.78
LY6E	8	143.9
EEF1D	8	144.4
TSTA3	8	144.5
RPL8	8	145.6
RPA1	9	19.4
ALDH3A2	9	36.8
SF3B2	9	38.4
7-Sep	9	72.8
ACTA2	9	72.9
TRA1	9	117.1
RPL35	9	121.1
HSPA5	9	121.5
LCN2	9	124.4
OAZIN	9	130.3
DPP7	9	133.4
PFKP	10	3.2
AKR1C1	10	5.1
PLAU	10	75.6
DSP	10	76.7
CBLB	10	123.2
TALDO1	11	0.434
CLTCL1	11	1.7
SLC22A1L	11	2.9
TSSC3	11	2.9
RPL27A	11	8.7
ST5	11	8.8
SAA1	11	116.6
MYOZ1	11	18.4

LDHA	11	18.5
ALDOA	11	33.7
MDK	11	46.4
EEF1G	11	62.6
REG1B	11	66.9
DOC-1R	11	67.5
GSTP1	11	67.6
DPEP1	11	95.1
MMP7	11	102.4
MMP12	11	102.8
GAB2	11	109.6
HYOU1	11	118.9
EHD3	12	1.6
SCNN1A	12	6.3
KRT8	12	51.6
KRT18	12	51.6
KRT7	12	52.3
KRT5	12	52.6
KRT6E	12	52.6
HADHA	12	55
ERBB3	12	56.2
NACA	12	56.8
RAB14	12	67.3
TM4SF3	12	71.2
NTS	12	86.2
CHAD	12	103.2
ASCL1	12	103.3
TXNRD1	12	104.6
CKAP4	12	106.6
COX6A1	12	120.7
BGN	12	122.5
RAN	12	129.88
RPL36A	14	48.1
PGD	14	50.7
MPZ	14	61.2
THBS2	15	37.5
TRAF4	15	38.3
SPINT1	15	38.7

RGN	15	42.8
RPL17	15	45.26
PKM2	15	70.1
CYFIP2	15	76.6
KIF21B	15	87.8
IDH2	15	88.2
RPL23A	16	0.377
MSLN	16	0.753
UBE2I	16	1.3
RPS2	16	1.95
CLDN9	16	3.1
ARL6IP	16	18.7
OSBPL1A	16	18.7
EIF3S8	16	28.3
TUFM	16	28.9
ALDOA	16	30.1
NME4	16	53.6
GPR56	16	57.4
CDH1	16	68.5
NQO1	16	69.5
SLC7A5	16	87.6
APRT	16	88.6
GALNS	16	88.6
RPL13	16	89.3
ARAF	17	4.7
PELO	17	19.6
MCP	17	32.4
ERBB2	17	35.11
KRT17	17	39.5
KRT19	17	39.6
JUP	17	39.8
CRF	17	40.39
RPL27	17	41.1
NME1	17	46.59
COL1A1	17	48.6
ABCC3	17	49.1
NME2	17	49.6
CLDN5	17	53.7

DCBLD2	17	71.4
RPL38	17	72.7
SMT3H2	17	73.6
SYNGR2	17	76.6
LGALS3BP	17	77.4
P4HB	17	80.3
PPAP2C	19	0.221
CD81	19	0.8
GPI	19	39.55
HPN	19	40.2
ZNF146	19	41.4
SPINT2	19	43.4
PSMD8	19	43.5
YIF1P	19	43.5
RPS16	19	44.6
SYNGR3	19	44.6
CEACAM5	19	46.9
CEACAM6	19	46.9
FOXP1	19	46.9
TUBE1	19	46.9
GIPR	19	50.8
SNRPD2	19	50.9
KDELR1	19	53.6
CAT	19	60.6
RPL28	19	60.6
RPS5	19	63.6
TRIM28	19	63.7
DAP	20	35.6
TOP1	20	40.3
LIPC	20	42.9
UBE2C	20	45.1
RAP2A	20	56.8
RPS21	20	61.6
EEF1A2	20	62.8
TFF3	21	42.6
TFF1	21	42.7
CSTB	21	44.1
FALZ	21	46.3

NR4A1	22	21.2
MIF	22	22.6
XBP1	22	27.5
DDX18	22	38.2
PRDX4	X	22.9
SYN1	X	46.3
TIMP1	X	46.3
LOC152185	X	47.2
PLP2	X	47.8
MAGED1	X	50.3
RPS4X	X	71
PGK1	X	75.4
RANBP1	X	77.2
SSR4	x	152.6

Table 4S. Sequences of the siRNAs.

EEF1A2mRNA sequence (NM_001958)	Antisense siRNA Oligonucleotide Template 5'AATAGGTGGACCCCCTCCCGGCCTGTCTC3'
	Sense siRNA Oligonucleotide Template 5'AACCGGGAGGGGGTCCACCTACCTGTCTC3'

KCIP-1 mRNA sequence (NM_003406)	Antisense siRNA Oligonucleotide Template 5'AACCCTGGGGACTACGACGTCCCTGTCTC3'
	Sense siRNA Oligonucleotide Template 5'AAGACGTCGTAGTCCCCAGGGCCTGTCTC3'